UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/866,279	05/30/97	DYMECKI	S 234805

HM12/0718
CUSHMAN DARBY & CUSHMAN
INTELLECTUAL PROPERTY GROUP OF
PILLSBURY MADISON & SUTRO LLP EAST TOW
1100 NEW YORK AVE N W NINTH FLOOR
WASHINGTON DC 20005-3918

EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	26

DATE MAILED: 07/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	08/866,279	DYMECKI, SUSAN M.	
	Examiner	Art Unit	
	Anne M. Baker	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 May 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *24* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed April 24, 2001 (Paper No. 25) has been entered. Claim 15 has been amended. Claims 1-49 remain pending in the instant application.

The following rejections are reiterated and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-49 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the previous Office Action mailed 10/25/00 (Paper No. 22), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

On page 2 of the response, Applicant argues that recombination resulting in gene activation is not essential to the invention's operability because cell marking and lineage tracing can be accomplished by recombination of an integrated DNA substrate and either direct detection of the recombined DNA substrate or deletion of a histochemical marker. The Examiner agrees that some of the claimed compositions and methods can be used for cell fate mapping. However, other aspects of the claimed invention require expression of the

target sequence after recombination occurs, while others require loss of expression. See, for example, Claims 35-42. Thus, many of the pending claims are not congruent with the utility of cell fate mapping.

On page 2 of the response, Applicant argues that Example 2 of the specification and particularly pages 39-40 disclose that recombination in the transgenic mice was site specific and precise. However, there is no discussion with regard to precision. The Examiner recalls that the Applicant made reference to some post-filing evidence with regard to the precision of *in vivo* recombination in the Interview of March 29, 2001. However, no further evidence has been submitted with regard to this. If Applicant wishes to argue that the *in vivo* recombination described in the specification is precise, it is suggested that Applicant submit this evidence in the form of a declaration in accordance with 37 CFR 1.132.

On page 3 of the response, Applicant argues that an organ or tissue showing chimerism or mosaicism in the number of Flp-recombination sequences may be used to trace cell lineages without requiring activation of gene expression. The Examiner agrees with this argument on its face, to the extent that such mosaics can be used for cell fate mapping. However, as noted above, many of the claims **do** require activation of gene expression.

On page 3 of the response, Applicant argues that Claim 11 involves the excision of a drug selectable marker gene, which allows a two-step selection scheme in producing transgenic mice by gene replacement using homologous recombination. However, as noted at page 5 of the previous Office Action (Paper No. 22), the specification reveals that in muscle, only 30% of the transgenes were in the recombined configuration as determined by Southern analysis (p. 40-41). Thus, only partial gene inactivation can be accomplished and the specification therefore does not demonstrate a phenotype produced by a deletion resulting in a null mutation because partial gene inactivation is not really a null mutation if only some cells have the deletion. This argument has not been addressed.

On page 3 of the response, Applicant argues that a "functional" recombination product is not necessary to achieve the objectives of translocation between chromosomes, excision of a gene to create a null mutation, and insertion of a transgene. Null mutations have already been addressed in the preceding paragraph. Further, the Examiner does not understand what the objectives are for translocation or insertion of a transgene, other than for gene activation. Gene activation **does** require a functional recombination product.

At page 3 of the response, Applicant argues that the invention can be used to activate expression of a transgene. Applicant points out that in Example 2, it was concluded on page 45 of the specification that "lack of βGal activity associated with the observed recombination most likely reflects a position effect on transgene transcription exerted by the genomic integration site since only one in four control FRTZ-product mouse lines expresses βGal." Applicant argues that hACTB regulatory sequences were not strong enough to direct transgene expression and that routine screening of additional lines of transgenic mice would identify a chromosomal integration site that supports a higher level of transgene expression. However, Applicant has not offered any support for this argument that screening would identify animals that exhibit detectable βGal activity. On page 5 of the previous Office Action (Paper No. 22), the Examiner pointed out that the specification states that "[i]mportantly, by screening additional FRTZ target loci, a chromosomal integration site has been identified that can support lacZ expression following Flp-recombination" (p. 45, lines 16-18). However, no further guidance is offered with regard to the critical element of producing functional recombination. This argument has not been addressed, yet Applicant continues to argue the criticality of chromosomal integration site without providing any support for their argument that routine screening will identify a mouse that works in the manner intended, wherein gene activation occurs.

On page 4 of the response, Applicant argues that XGal staining to detect βGal activity is not a sensitive assay for detecting recombination events and gene activation. Applicant goes on to argue that Southern blotting or PCR amplification with primers that detect the recombined target locus is a sensitive assay to detect recombination events. While Southern blotting and PCR analysis can be used to detect recombination events, it cannot be used to detect gene activation. In the experiments conducted in the specification, XGal staining to detect βGal activity is the **only** assay that was used to detect gene expression at the protein level. Thus, the availability of more sensitive assays for detecting recombination does not support Applicant's initial argument beginning on page 3, paragraph 5, that "the invention can be used to activate expression of a transgene."

On page 4 of the response, Applicant argues that activation of gene expression may be accomplished by choosing a transgene with greater biological activity (e.g., a more active Flp recombinase or other genes whose biological effects are easier to detect than βGal) or a regulatory sequence that is stronger than that of the human β-actin gene. Applicant points to pp. 15-17 for teaching other regulatory regions that may be used in the invention. Applicant suggests that a regulatory region from the HMG-CoA reductase gene can be used as an alternative to the β-actin regulatory region used in Example 2. Applicant goes on to discuss the use of FLP recombinase with enhanced thermostability (FLPe) and the Hmgcr regulatory region as described in Rodriguez et al. (2000) Nature Genet. 25: 139-140. Applicant points to the teachings of the specification at page 15 for teaching that FLPe is a Flp transgene. However, the specification does not provide any teachings with regard to FLPe. The Examiner does not find that FLPe was known in the art at the time of filing of the instant specification. Thus, post-filing evidence that relies on the use of FLPe cannot provide enablement support for the claimed invention, as the use of FLPe cannot be derived from the teachings of the specification. The instant specification was filed 5/30/97, while the publication disclosing the production of

the enhanced version of FLP recombinase known as FLP was published in July 1998. At page 15 of the specification, the disclosure only states that "[e]xamples of Flp variants are given in Kulpa et al., (1993)." However, Kulpa et al. does not teach the FLPe recombinase used in the studies of the post-filing art. The specification broadly discloses the use of variant forms of FLP recombinase, but does not disclose the use of a thermostable FLP recombinase, nor does it disclose the criticality of using a thermostable recombinase to enable the claimed invention. The Examiner recalls that in the Interview of March 29, 2001, Applicant referred to a different publication, that of Rodriguez et al. (2000) Neuron 27: 475-786 (hereinafter, "Neuron"), that described activation of the βGal gene for cell lineage marking. Given the arguments provided at page 4 of the response, the Examiner is now confused as to whether Applicant can attest to the fact that the FLPe recombinase gene was **not** used in the Neuron studies. The Experimental Procedures section at page 483 indicates that some of the experiments disclosed therein were conducted using the F70L version of FLP recombinase, which the Examiner understands to be the same recombinase version used in the examples of the specification. Given the reliance in the response on the use of the FLPe recombinase gene, the Examiner is unclear as to whether there is a discrepancy in the disclosure of the Neuron paper regarding the version of FLP recombinase used in those studies. If Applicant prefers to rely on the disclosure of the Neuron paper, it is suggested that a Declaration in accordance with 37 CFR 1.132 be submitted clarifying the conditions of the experiments conducted therein, particularly with regard to the recombinase version used and the integration technique used. Regarding the integration technique used, the Examiner is unclear as to whether targeted integration was used to obtain the reported results. The specification states on p. 45 that a chromosomal integration site was identified, but no further information is provided with regard to the identity of the site. The Examiner does not find that the results reported in the Nature Genetics paper of Rodriguez et

al. (2000) can be derived from the teachings of the specification due to the use of the FLPe recombinase, a recombinase version not available or known in the art at the time of filing of the instant specification.

If the results reported by Rodriguez et al. (2000; Neuron 27: 475-486) were obtained using the same methodology (e.g., same FLP recombinase, same random integration of transgene constructs, etc.) disclosed in the specification with only the exception that a different promoter was used on the transgene constructs, then the Examiner agrees that one could take the teachings of the specification and, using routine experimentation, swap out the promoter used to drive expression of the FLP recombinase and/or the recombination product to obtain the results reported by Rodriguez et al. (2000). If, however, further manipulations of the system were required to produce those results (such as targeting the transgenes to specific chromosomal loci), then Applicant is invited to point to the requisite teachings in the specification for carrying out said further manipulations. A Declaration under 37 CFR 1.132 clarifying these issues is suggested.

At page 4 of the response, Applicant argues that activation of transgene expression can be achieved, and that the transgenic mice of Example 2 can be modified "in a manner taught in the specification and predicted by Applicant to show such gene activation." The Examiner awaits the submission of appropriate evidence with regard to the necessary modifications. The Examiner cannot further comment on evidence not of record and so cannot evaluate whether said modifications are indeed taught in the specification.

At page 5 of the response, Applicant again argues that recombination is precise. This argument has already been addressed herein above. There is no evidence of record showing precise recombination. If evidence is available, Applicant is invited to submit the evidence in the form of a Declaration in accordance with 37 CFR 1.132.

At page 5 of the response, Applicant argues that cell lineage marking is a specific utility for the claimed invention. The Examiner agrees and awaits further evidence regarding **enablement** for this utility.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 1630